

Abstract

Grant Number: 1 X01 MH077633-01

PI Name: REED, JOHN C

PI Email: reedoffice@BURNHAM.ORG

PI Title: PROFESSOR, PRESIDENT AND CEO

Project Title: Chemical inhibitors of antigen receptor-induced NF- κ B activation

Abstract: *DESCRIPTION* (provided by applicant): Many cellular pathways leading to activation of NF- κ B-family transcription factors have been identified, participating in host-defense, immunity, inflammation, and cancer. Recently, a unique pathway activated by antigen receptors on T- and B-lymphocytes has been revealed, involving a cascade of participating proteins that includes CARMA1 (Blimp), Bcl-10, paracaspase (MALT1), TRAF6, and Ubc13. This pathway is initiated by Protein Kinase C- θ , which induces phosphorylation of components of this signaling pathway. Treatment of cells with the combination of phorbol ester PMA and calcium-ionophore ionomycin triggers this pathway, resulting in NF- κ B activation. We have devised a stably transfected reporter cell line that contains a luciferase gene driven by a NF- κ B responsive promoter. In pilot studies, we have used this cell-based assay to screen collections of compounds, confirming suitable assay performance for the high throughput environment. Hits from this screen are counter-screened using the same reporter cell line stimulated with alternative NF- κ B activators, including TNF α , thus identifying pathway-specific chemical inhibitors. We propose to use this cell-based HTS assay for screening the NIH's chemical library. The compounds identified using this assay will be useful research tools for analysis of the physiological roles of this NF- κ B activation pathway.

Thesaurus Terms:

High throughput screening, Chemical inhibitors, antigen receptor, NF- κ B, T- and B-lymphocytes, CARMA1, Blimp, Bcl-10, paracaspase (MALT1), TRAF6, Ubc13, Protein Kinase C- θ , phorbol ester PMA, calcium-ionophore ionomycin, luciferase, TNF α , cell-based HTS assay

Institution: BURNHAM INSTITUTE FOR MEDICAL RESEARCH
REED LAB
10901 NORTH TORREY PINES ROAD
LA JOLLA, CA 92037

Fiscal Year: 2006

Department: DEPARTMENT OF PATHOLOGY

Project Start: 2006/02/01

Project End: 2007/01/31

ICD: NATIONAL INSTITUTE OF MENTAL HEALTH

IRG: ZMH1